REMARKS

Claims 1-8, 14, 15, 19, 32, 33, 36-52, 55, 58 and 59 are pending in the present application. Claims 19, 40-45, 58 and 59 have been withdrawn. By virtue of this response, claims 14, 15, 36, 39, 48, 49 and 55 have been cancelled, and claim 1 has been amended. Support for the amendment of claim 1 is found in the specification, such as at page 45, lines 5-8, and page 46, lines 26-33. Accordingly, claims 1-8, 32, 33, 37, 38, 46, 47, 50, 51, and 52 are currently under consideration.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Claims Rejection – 35 U.S.C. § 103(a)

Claims 1-8, 14-15, 32-33, 36-39, 46-52 and 55 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Siegall et al. (U.S. Patent No. 6,843,989) (892; of record) in view of Li et al. (U.S. Patent No. 6,495,129), Hanna et al. (US 2001/0018041 A1) and Grillo-Lopez (U.S. Patent No. 6,455,043) (892; of record), Benoit et al. (Immunopharmacology 35: 129-139, 1996) (1449; #59) essentially for the reasons of record and in further view of Strom et al. (in Therapeutic Immunology, edited by Austen et al., Blackwell Science, Cambridge MA, 1996; see pages 451-456) (1449; #6), Hollingsworth ("Seattle Genetics; SGN40 Still Alive After Lymphoma Bust", BioWorld Today-20(192): 1, 4, October 6, 2009) and Seattle Genetics News Release ("Seattle Genetics Announces Discontinuation of Dacetuzumab Phase lib Diffuse Large B-Cell Lymphoma Clinical Trial", October 5, 2009) 9 (1449; #1).

Applicants respectfully traverse this rejection and reiterate arguments made in the previous responses.

Claim 1 as amended is directed to a method for treating a neoplastic disease or disorder characterized by cells expressing CD40 in a mammal, comprising: administering to the mammal a

rituximab and an anti-CD40 antibody that binds and stimulates CD40, enhances interaction between CD40 and CD40L and arrests the growth of or causes deletion of cells expressing CD40, wherein the anti-CD40 antibody is a monoclonal antibody that specifically competes for binding of CD40 with antibody S2C6, wherein the neoplastic disease or disorder is rituximab resistant, and wherein rituximab and the anti-CD40 antibody in combination inhibits the neoplastic disease or disorder in said mammal. Claims 2-8, 32, 33, 37, 38, 46, 47, 50-52 depend from claim 1. Claims 14, 15, 36, 39, 48, 49, and 55 have been canceled.

The factual inquires in the obviousness determination as set forth in *Graham v. John Deere Co.* (383 U.S. 1, 17 (1966)) are as follows: (1) the scope and content of prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the pertinent art, and (4) secondary considerations such as commercial success, long-felt need, and unexpected results. The Supreme Court in *KSR* reaffirmed that the *Graham* factual inquiries still control an obvious inquiry, but explained that the Federal Circuit's "teaching, suggestion or motivation" test provides helpful insight into the obviousness question as long as it is not applied rigidly. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

Applicants respectfully submit that the references cited by the Examiner, even if combined, do not teach or suggest the use of a combination treatment with an anti-CD40 antibody and rituximab in treating a rituximab resistant neoplastic disease. Although the references cited by the Examiner indicated that an anti-CD20 antibody or an anti-CD40 antibody might be effective in treating a neoplastic disease, none of the references recognized that a combination treatment with an anti-CD40 antibody and rituximab would provide benefit in treating a rituximab resistant neoplastic disease.

In addition, one skilled in the art would not have been motivated to combine the teachings of these references to arrive at the claimed invention and would not have a reasonable expectation of success for using rituximab in combination with an anti-CD40 antibody for treating a rituximab resistant neoplastic disease. As demonstrated in Example I of the present application, rituximab resistant Ramos lymphoma cell line was established through exposing the Ramos lymphoma cell line to high doses of rituximab (500 ug/mouse IP, 3 times/week for 3 weeks) in a

subcutaneous xenograft SCID mouse. This indicates that the lymphoma cell line used in this model was resistant to rituximab treatment at 25 mg/kg dose if the body weight of the mouse was about 20 g. As shown in Figure 5, the anti-CD20 antibody rituximab alone (at 4 mg/kg, total 9 doses) had not significantly reduced the rate of tumor volume increase and all mice in this treatment group died or were forced to sacrifice because of the tumor size after 24 days post treatment. The anti-CD40 antibody (at 4 mg/kg, total 9 doses) treatment had reduced the rate of tumor volume increase, but only 1/10 mice treated with the anti-CD40 antibody was tumor free. In contrast, 10/10 mice treated with both the anti-CD40 antibody and the anti-CD20 antibody (4 mg/kg each, total 9 doses) were tumor free. One skilled in the art would not have expected that additional effect could be achieved for a combination treatment with an anti-CD40 antibody and rituximab for tumor cells that are resistant to rituximab treatment. Since the references cited by the Examiner did not recognize or appreciate this beneficial effect achieved by the combination of the anti-CD40 antibody and rituximab, one skilled in the art would not have the motivation to use this combination treatment for treating a neoplastic disease that is resistant to one of the treatment in the combination and would not have had a reasonable expectation of success.

The Examiner states that "[i]t is well settled that 'discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Citing *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980); *Merck & Co. v. Biocraft Labs. Inc.*, 874 F.2d 804, 80910 USPQ2d 1843, 1847-48 (Fed. Cir. 1989). The Examiner further states that "[a]s dosing of combination therapy with agents that target different molecular targets resulting in additive-synergistic effects were known to the ordinary artisan, it would have been obvious to optimize both the dosing regimens and mode of administration to meet the needs of the patient at the time the invention was made." Applicant respectfully disagrees with the Examiner.

Applicant respectfully notes that the Examiner is applying an improper "obvious to try" rationale in support of the obviousness rejection. Under *KSR*, when one skilled in the art is faced with "a finite number of identified, predictable solutions" to a problem, and pursues "the known options within his or her technical grasp", the resulting discovery "is likely the product not of innovation but of ordinary skill and common sense." *KSR*, 127 S. Ct. at 1742. However, "courts

should not succumb to hindsight claims of obviousness" when researchers can only "vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful. See *Procter & Gamble*, 566 F.3d at 996, citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), and *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

Applicant respectfully submits that a large number of choices (including various chemotherapies, radiotherapies, antibody therapies, etc.) were available for one skilled in the art to select and design a combination treatment for a neoplastic disease characterized by cells expressing CD40. The references cited by the Examiner, considered as a whole, gave only general guidance for combination therapies, but provide no indication of which specific combination therapy was likely to provide additional benefit to a patient as compared to a single therapy. One skilled in the art could not predict which combination of anti-cancer treatments could provide additive-synergistic effects, and not every combination of anti-cancer treatments resulted in additive-synergistic effects. Further, as discussed below, data in Hanna et al. cited by the Examiner taught away from using a combination of an anti-CD20 antibody and an anti-CD40 antibody which stimulates CD40 and enhances the interaction between CD40 and CD40L as claimed in the present application to treat a neoplastic disease characterized by cells expressing CD40. Considering the large number and complexity of the alternatives faced by the skilled artisan and the unpredictability of the field, Applicant respectfully submits that the Examiner's conclusion of obviousness is based on improper hindsight reasoning.

The Examiner further states that "the prior art would be consistent with employing different type of anti-CD40 antibodies, such as antagonist and agonist antibodies, antibodies that bind to different epitopes, unconjugated antibodies and antibodies conjugated to a cytotoxic agent, provided such antibodies (e.g., anti-CD40 antibodies or anti-CD20 antibodies in this particular case) targeted the appropriate markers (e.g., CD40, CD20) and inhibited the interactions and functions mediated via such markers or the cells expressing said markers in order to inhibit undesirable immune response, including undesirable immune response such as those associated with neoplastic

disorders encompassed by the claimed invention." Applicant respectfully disagrees with the Examiner. Applicant respectfully notes that an "antagonist" and an "agonist" generally have opposite functions. If an antagonist has a certain effect on a cell, one skilled in the art would not expect that an agonist would have the same effect on the same cell. Hanna et al. cited by the Examiner showed that CD40L-CD40 signaling prevented apoptosis of B-lymphoma cells induced by anti-CD20 antibody rituximab. See Example 3, Table 1. The data in this reference indicated that activation of the CD40L-CD40 pathway by the soluble CD40L generated resistance of rituximab induced apoptosis in DHL-4 lymphoma cells. Accordingly, the combination treatment with soluble CD40L and rituximab might not provide even additive effects as compared to treatment with each molecule alone. In view of the data, one skilled in the art would not be motivated to select an anti-CD40 antibody (such as antibody S2C6) having similar activities as a soluble CD40L for a combination treatment with an anti-CD20 antibody for treating a neoplastic disease characterized by cells expressing CD40, and would not reasonably expect that this combination would have at least additive effects for treating the neoplastic disease. This reference cited by the Examiner is not consistent with selecting the specific type of anti-CD40 antibody recited in the claims of the present application to use in a combination therapy with an anti-CD20 antibody.

The Examiner further states that Applicant's arguments in conjunction with the Declaration by Dr. Lewis based upon the reliance of the SCID animal model is inconsistent with the clinical results. Applicant respectfully disagrees with the Examiner. Applicant respectfully notes that the clinical trial disclosed in the Seattle Genetics News Release and the BioWorld Today article is a trial involving a treatment with dacetuzumab (an anti-CD40 antibody) in combination with rituximab plus ifosfamide, carboplatin and etoposide (R-ICE) chemotherapy for patients with relapsed or refractory diffuse large B-cell lymphoma. The treatment regimen in this trial is different from the treatment regimen used in the SCID animal model presented in the Declaration by Dr. Lewis. Different clinical regimen may result in different clinical efficacy.

In view of the above, Applicant respectfully submits that claims 1-8, 32, 33, 37, 39, 46, 47, and 50-52 are not obvious over Siegall et al. in view of Li et al., Hanna et al., Grillo-Lopez,

Benoit et al., and further in view of Strom et al., Hollingsworth et al, and Seattle Genetics News Release. Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 146392002400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: May 24, 2010

Respectfully submitted,

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